15:44:24 OCA PAD INITIATION - PROJECT HEADER INFORMATION 10/04/93

Active

Project #: G-33-550 Cost share #: Rev #: 0
Center # : 10/11-6-P5238-2A0 Center shr #: OCA file #:
Work type : INST
Contract#: 5 F31 AG05614-02 Mod #: Document : GRANT
Prime #: Contract entity: GTRC

Subprojects ? : N CFDA:
Main project #: PE #:

Project unit: CHEMISTRY Unit code: 02.010.136
Project director(s):
POWERS J C CHEMISTRY (404)894-4038

Sponsor/division names: DHHS/PHS/NIH / NATL INSTITUTES OF HEALTH
Sponsor/division codes: 108 / 001

Award period: 931001 to 940930 (performance) 941230 (reports)

Sponsor amount	New this change	Total to date
Contract value	11,491.00	11,491.00
Funded	11,491.00	11,491.00
Cost sharing amount		0.00

Does subcontracting plan apply ?: N

Title: ACETYLCHOLINESTERASE INHIBITORS AND DEMENTIAS

PROJECT ADMINISTRATION DATA

OCA contact: E. Faith Gleason 894-4820

Sponsor technical contact

DR. CARL BANNER
(301)496-9350

NATIONAL INSTITUTE ON AGING
NATIONAL INSTITUTES OF HEALTH
5333 WAESTBARD AVE
BETHESDA, MD 20816

Sponsor issuing office

JOANNE COLBERT
(301)496-1472

NATIONAL INSTITUTE ON AGING
GRANTS & CONTRACTS
GATEWAY BUILDING
7201 WISCONSIN AVE., SUITE 2N-212
BETHESDA, MARYLAND 20892

Security class (U,C,S,TS) : U ONR resident rep. is ACO (Y/N): N
Defense priority rating : PHS supplemental sheet
Equipment title vests with: Sponsor GIT X
NONE AUTHORIZED
Administrative comments -
INITIATION OF INDIVIDUAL NATIONAL RESEARCH SERVICE AWARD - 2ND YEAR.

GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION

NOTICE OF PROJECT CLOSEOUT

Closeout Notice Date 10/24/94

Project No. G-33-550 Center No. 10/11-6-P5238-2A0

Project Director POWERS J C School/Lab CHEMISTRY

Sponsor DHHS/PHS/NIH/NATL INSTITUTES OF HEALTH

Contract/Grant No. 5 F31 AG05614-02 Contract Entity GTRC

Prime Contract No.

Title ACETYLCHOLINESTERASE INHIBITORS AND DEMENTIAS

Effective Completion Date 940930 (Performance) 941230 (Reports)

Closeout Actions Required:	Y/N	Date Submitted
Final Invoice or Copy of Final Invoice	Y	
Final Report of Inventions and/or Subcontracts	Y	
Government Property Inventory & Related Certificate	N	
Classified Material Certificate	N	
Release and Assignment	N	
Other	N	

Comments
***NOTE: USE DHHS FORM FOR PATENT ***

Subproject Under Main Project No.

Continues Project No.

Distribution Required:

Project Director	Y
Administrative Network Representative	Y
GTRI Accounting/Grants and Contracts	Y
Procurement/Supply Services	Y
Research Property Managment	Y
Research Security Services	N
Reports Coordinator (OCA)	Y
GTRC	Y
Project File	Y
Other	N
	N

NOTE: Final Patent Questionnaire sent to PDPI.

USE THIS LABEL TO RETURN APPLICATION

VIDUAL NATIONAL RESEARCH SERVICE AWARD CONTINUATION APPLICATION

OMB No. 0925-0002

5 F31 AG05614-02
NATIONAL INSTITUTE ON AGING
GRANTS & CONTRACTS
GATEWAY BUILDING
7201 WISC. AVE. SUITE 2N-212
BETHESDA, MARYLAND 20892

REVIEW GROUP	TYPE	ACTIVITY	FELLOWSHIP NUMBER
SRC -7	5	F31	AG05614-02

TOTAL AWARD PERIOD
From: 10/01/92 Through: 09/30/96

REQUESTED BUDGET PERIOD
From: 10/01/93 Through: 09/30/94

e verified by applicant. Check information in Items 1 through 6. If incorrect, furnish correct information in Item 11.

TLE OF RESEARCH TRAINING PROPOSAL

ACETYLCHOLINESTERASE INHIBITORS AND DEMENTIAS

APPLICANT *(Name and address, street, city, state, zip code)*

STARKS, KENNETH M
GEORGIA INST OF TECHNOLOGY
SCH OF CHEMISTRY & BIOCHEM
ATLANTA, GA 30332-0400

4. SPONSORING INSTITUTION *(Name and address, street, city, state, zip code)*

GEORGIA TECH RES CORP
GEORGIA INST OF TECH
ATLANTA, GA 30332

5. ENTITY IDENTIFICATION NUMBER
158060314GA1

SOCIAL SECURITY NUMBER

2c. HIGHEST DEGREE(S)
BA

6. TITLE AND ADDRESS OF OFFICIAL SIGNING FOR SPONSORING INSTITUTION
xxxxxxxx IN BUSINESS OFFICE
Janis Goddard
CONTRACTING OFFICE
GEORGIA TECH RES CORP
GEORGIA INST OF TECHNOLOGY
ATLANTA, GA 30332-0420

DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT
SCHOOL OF CHEMISTRY & BIOCHEM

MAJOR SUBDIVISION
COLLEGE OF SCIENCES

NAME OF SPONSOR
POWERS, JAMES C

BITNET/INTERNET ADDRESS

plete the following *(See instructions)*

HUMAN SUBJECTS
☒ NO ☐ YES { ☐ Exemption # _____ OR ☐ IRB Approval Date _____
Assurance of Compliance # _____

10a. PERMANENT MAILING ADDRESS *(Street, city, state, zip code)*

3546 Heritage Valley Rd.
Atlanta, Georgia 30331

VERTEBRATE ANIMALS
☒ NO ☐ Yes... IACUC Approval Date _____
Animal Welfare Assurance # _____

RAINING SITE(S) (Organizations and Addresses)

10b. APPLICANT'S TELEPHONE INFORMATION

	Area Code	Phone number & extension
OFFICE	404	894-3286
FAX	404	894-7452
HOME	404	350-8244
PERMANENT ADDRESS	404	346-1862

USE THIS SPACE FOR CORRECTIONS TO ITEMS 1 THROUGH 6. INDICATE THE NUMBER(S) WHERE ANSWERS APPLY.

APPLICANT CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, accurate, and complete to the best of my knowledge, I agree to comply with Public Health Service terms and conditions if an award is issued as a result of this application. I certify that I have read the National search Service Award Service Assurance, that I will abide by the Assurance if an award is made, and that the award will not support residency training. Willful vision of false information is a criminal offense (U.S. Code, Title 18, Section 1001). I am aware that any false, fictitious, or fraudulent statement may, in addition other remedies available to the Government, subject me to civil penalties under the Program Fraud Civil Remedies Act of 1986 (45 CFR Part 79).

GNATURE [redacted] DATE 07-15-93

S 416-9 (Rev. 10/91) OPTIONAL

COMPLETE AND RETURN APPLICATION BY 1 AUGUST 1993

INDIVIDUAL NATIONAL RESEARCH SERVICE AWARD
CONTINUATION APPLICATION

FELLOWSHIP NUMBER

AG05614-02

APPLICANT SUMMARY OF ACTIVITIES *(Do not exceed 3 pages.)*

A. CHANGES
Since submission of the last application, have any significant changes occurred in the training program, particularly the research project, academic status, or time distribution of activities *(i.e., percentage of time devoted to research project, course work, teaching, etc.)*? If so, explain.

B. PROGRESS REPORT
Describe concisely the research performed and research training obtained during the past year. List all courses and publications.

C. RESEARCH TRAINING PLANS
Describe concisely the research and research training planned for the requested budget period, including any course work.

13. APPLICANT SUMMARY OF ACTIVITIES

A. CHANGES

There have not been any alterations in the focus of the research or the training plan of the student since the original proposal.

B. PROGRESS REPORT

During the past academic year at Georgia Tech I have been working diligently to complete both the synthesis of specific low molecular weight inhibitors of acetylcholinesterase as well as the curriculum of required courses set forth by Georgia Tech. I have satisfied the course requirements for matriculation by successfully completing courses in Advanced Physical Organic Chemistry, Macromolecular Structure, and Immunochemistry and I am a student in good standing.

The research plan that I proposed called for the synthesis of derivatives which would improve the specificity, potency and hydrophobicity of compound **1** which has been previously synthesized by the Powers group. I have made significant progress towards completing the goals that I have set and I expect to finalize the synthesis of several compounds for testing before the end of the summer quarter 1993. Compound **2** has been synthesized and shown to inhibit acetylcholinesterase *in vitro*.

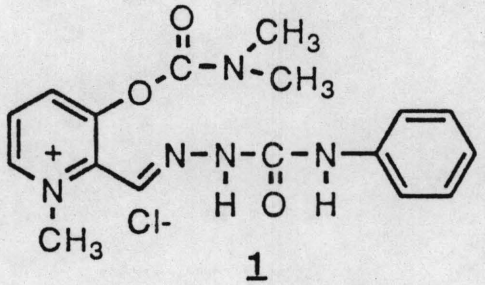
The first step in the synthesis of these analogs requires a 3-hydroxypicolinaldehyde (**4**) which can be synthesized by a variety of methods. I have made this compound several times by using a large excess of MnO_2 and acetone at room temperature. The yields for this reaction are typically low with the highest yield being approximately 51%. This reaction has however proven to be unreliable at times because of the sensitivity to inactivation of the MnO_2 catalyst. I am interested in carrying out other literature procedures to synthesize this aldehyde that do not require MnO_2 but proceed by rearrangement and hydrolysis of 3-hydroxypicolinaldehyde triacetate (**3**). This alternative should provide a better yield as well as improve the repeatability of the experiment.

Phenyl semicarbazide derivatives (**6**) have been synthesized by reacting the appropriately substituted phenyl isocyanate (**5**) with a 10 fold excess of hydrazine monohydrate in methylene chloride at zero degrees. The products are easily isolated by suction filtration. This method has produced several substituted phenylsemicarbazides which include: 2,6-dichloro, 4-chloro, 2,6-dimethyl, 2,6-difluro, 4-methoxy, 4-nitro, and 3-nitro. The yields for these reactions are typically in the low eighties with the highest yield being 88% obtained from the 2,6 dimethyl derivative.

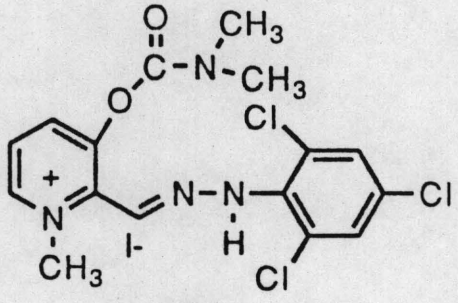
The synthesis of pyridine semicarbazones (7) and hydrazides (compound **2** is an example of a hydrazide) have been carried out by reacting the appropriate phenylsemicarbazide or phenylhydrazide with the pyridine aldehyde in ethanol at reflux temperature for one hour. The clean products are isolated by suction filtration. Yields for this reaction are generally 70-75%. The Schiff base analogs are then carbamylated by using pyridine and dimethylcarbamyl chloride at room temperature for 14 hours with subsequent methylation of the pyridinal nitrogen by methyl iodide then ion exchange by silver chloride. The carbamylation reaction yields up to 85% of its products while the yield for the salt ion exchange has not been determined.

C. RESEARCH TRANING PLAN

During the upcoming budget period I will be synthesizing more derivatives of compound **1** as potential acetylcholinesterase inhibitors. I will also be testing my compounds for their effectiveness by *in vitro* assays that have been worked out by the Power's group. All of the compounds that are deemed successful will be tested in animal models by a team of behavioral pharmacologists at The Medical College of Georgia. In the future we plan to submit the results of our joint investigations for publication.

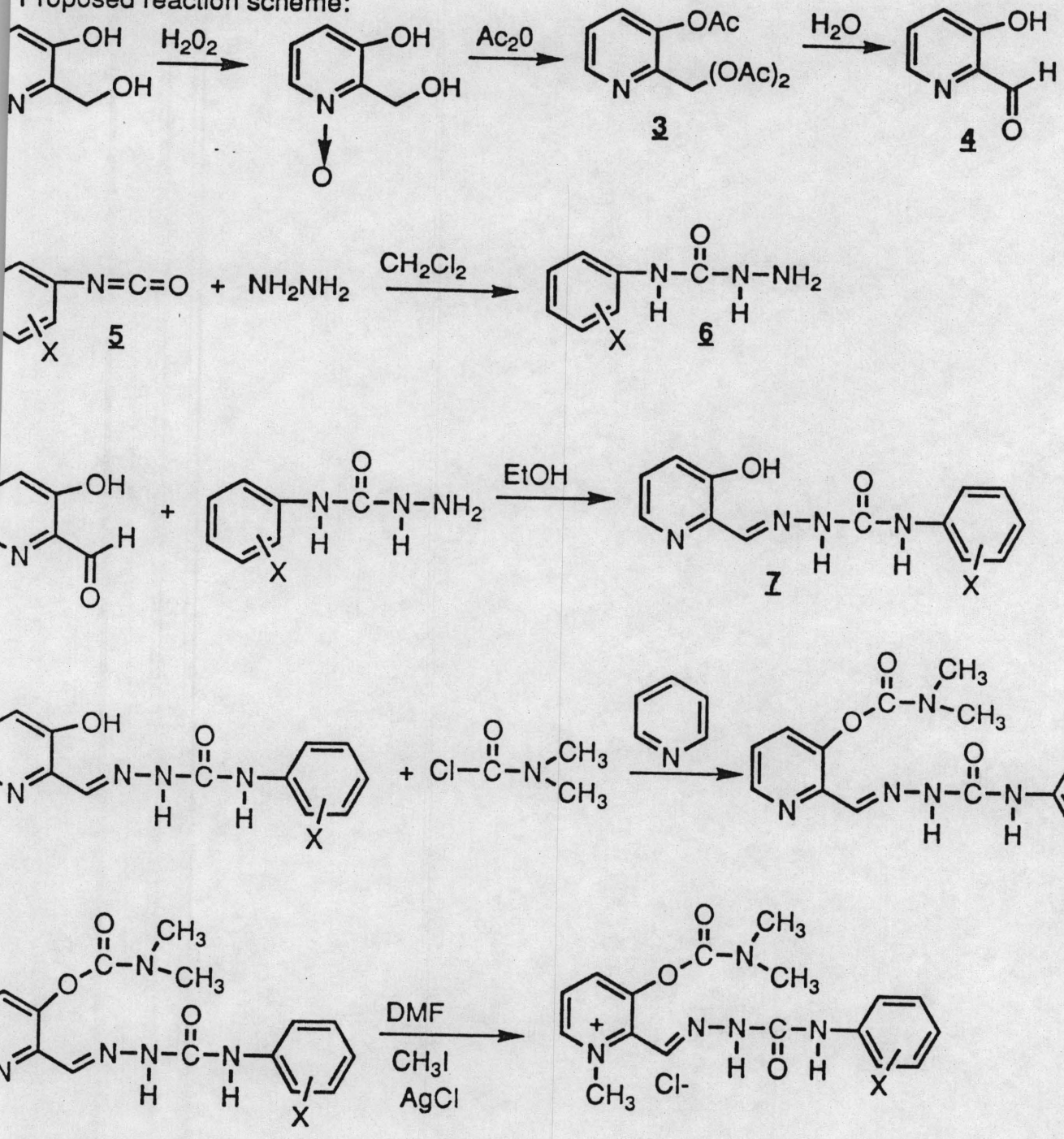


1



2

Proposed reaction scheme:



t II

INDIVIDUAL NATIONAL RESEARCH SERVICE AWARD CONTINUATION APPLICATION

(To be completed by sponsor—follow instructions)

FELLOWSHIP NUMBER: AG05614-02

SUPPLEMENTATION OF FELLOW: ☐ NO ☒ YES — If "yes," specify the amount(s) and dates on which supplementation occurred, and the source of the funds.

COMMENTS OF SPONSOR *(Use additional page, if necessary)*

A. Evaluate the quality of the training (including academic work) and research progress made by the fellow during the past year. Include performance on cumulative and qualifying examinations, if applicable.

B. Human subjects and vertebrate animals *(see instructions).*

15A. Ken received low grades in his courses in the fall quarter of 1992 and was placed on probation during the winter quarter of 1993. During the spring quarter of 1993, he received good grades in several courses and returned to normal graduate student status (good standing). He has decided to complete a Masters degree in chemistry before continuing with his graduate studies. He has now completed all of the necessary course work and must simply complete enough research work for a Masters thesis. I expect Ken to complete sufficient research for a Masters thesis sometime during the next year.

Ken's research progress to date has been satisfactory, but quite slow. He works consistently in the laboratory and is enthusiastic and interested in his research problem. He is very interested in the research field and is reading constantly in the area. However, he had taken a long time to learn synthesis skills and is still learning how to effectively perform techniques as simple as the recrystallization of reaction products. As he progresses, Ken is slowly making more of these skills part of his repertoire. He is beginning to work out the synthetic methods for the synthesis of the proposed acetylcholinesterase inhibitors (see progress report). He has now synthesized his first final inhibitor structure. Since he plans to synthesize a number of closely related derivatives to complete his thesis work, the remainder of the compounds should be more easily and quickly synthesized now that he has worked out the methods with the first derivative.

15B. No human subjects or vertebrate animals are involved in this research.

vide the number of subjects enrolled in the study *to date* according to the following categories (see Page 6 for definitions).

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	TOTAL
ıale							
e							
nown							
TAL							

CERTIFICATION. We, the undersigned, certify that: (a) the information herein, including involvement of Human Research Subjects, Recombinant DNA Research, and Vertebrate Animals, are true, accurate, and complete to the best of our knowledge; (b) if this application results in an award, appropriate training, adequate facilities, and supervision will be provided; and (c) we will comply with the Public Health Service terms and conditions of award. A willfully false certification is a criminal offense (U.S. Code Title 18, Section 1001). We are aware that any false, fictitious, or fraudulent statement may, in addition to other remedies available to the Government, subject us to civil penalties under the Program Fraud Civil Remedies Act of 1986 (45 CFR Part 79).

SIGNATURE	TYPED NAME	OFFICE TELEPHONE	DATE
ONSOR	James C. Powers	894-4038	7/27/93
ARTMENT HEAD	Laren M. Tolbert	894-4002	7/29/93
FICIAL SIGNING FOR SPONSORING INSTITUTION	Janis L. Goddard	404/894-4817	7/30/93

14. The fellow was given a supplement of $295/month from a seed grant from the Georgia Tech/Medical College of GA seed grant program. The amount is the difference between the normal stipend of $13,000/year for chemistry graduate students and the amount provided by the NIH fellowship.

INDIVIDUAL NRSA CONTINUATION APPLICATION CHECKLIST

Applicant completes Section I. Sponsor completes Section II.

FELLOWSHIP NUMBER

AG05614-02

tion I—Applicant

SURANCES/CERTIFICATIONS

following assurances/certifications are made by checking the appropriate boxes and are verified by your signature in Item 12 on the CE PAGE of the application. Descriptions of individual assurances/certifications begin on page 2 of the application instructions.

Debarment and Suspension [X] No [ ] Yes *(Attach explanation)*

Delinquent Federal Debt [X] No [ ] Yes *(Attach explanation)*

tion II—Sponsoring Institution

following assurances/certifications are made by checking the appropriate boxes and verified by the signature of the Official Signing for nsoring Institution in Item 16. Descriptions of sponsoring institution assurances/certifications begin on page 7 of the application instructions.

Human Subjects *(Complete Item 7 on the Face Page)* [ ] Full IRB Review [ ] Expedited Review

Use of Human Subjects: [ ] Change [ ] No Change Since Previous Submission

Vertebrate Animals *(Complete Item 8 on the Face Page)*

Use of Vertebrate Animals: [ ] Change [ ] No Change Since Previous Submission

Debarment and Suspension [X] No [ ] Yes *(Attach explanation)*

Misconduct in Science (Form PHS 6315) [X] Filed [ ] Not Filed

If filed, date of Initial Assurance or latest Annual Report. 1/14/92

Civil Rights (Form HHS 441) [X] Filed [ ] Not Filed

Handicapped Individuals (Form HHS 641) [X] Filed [ ] Not Filed

Sex Discrimination (Form HHS 639A) [X] Filed [ ] Not Filed

Age Discrimination (Form HHS 680) [X] Filed [ ] Not Filed

Final Report

National Research Service Award to

Kenneth M. Starks

F31 GM15612

October 1, 1992 to September 1, 1994

Research Supervisor

James C. Powers
School of Chemistry and Biochemistry
Georgia Institute of Technology
Atlanta, GA 30332-0400
(404)894-4038

Research Summary

The carbamate 1-(methyl-3-(N,N-dimethylcarbamoyloxy)-2-pyridylmethylene)-4-(4-phenyl)diazinecarboxamide chloride (MHP 133) is the parent for a new class of pyridinium salts which inhibit acetylcholinesterase (AChE) *in vitro* as well as *in vivo*. Fourteen new derivatives of MHP 133 have been synthesized with the intention of improving their hydrophobicity while maintaining their propensity to inhibit acetylcholinesterase. Upon prolonged incubation with AChE, the pyridinium salts exhibit progressive time-dependent inhibition according to first order kinetics with $k_{obs}/[I]$ values ranging from 3 to 345 $M^{-1}s^{-1}$. The enzyme didn't regain any activity after prolonged incubation with the inhibitors (1 day). The partition coefficients for each inhibitor were evaluated in octanol/water in order to determine their hydrophobic character as hydrophobicity is a key prerequisite for crossing the blood brain barrier.

National Research Service Award to Kenneth M. Starks

F31 GM15612

Patent Applications:

Pyridinium Compounds, J. C. Powers, J. L. Buccafusco, K. L. Starks (1994) filed February 1994.

Publications:

Novel Pyridinium Derivatives as Inhibitors for Acetylcholinesterase, Starks, K. M., Ortega-Vilain, A.-C., Buccafusco, J. J., and Powers, J. C. (1995) *J. Enzyme Inhibition*, submitted.